USE OF ANTIMICROBIAL PEPTIDES AS PRESERVATIVES IN OPHTHALMIC PREPARATIONS, INCLUDING SOLUTIONS, EMULSIONS, AND SUSPENSIONS

Background of the Invention

This invention relates to preserved ophthalmic compositions. More particularly, the present invention relates to preserved ophthalmic compositions, for example, useful in administering a therapeutic component to the eyes, and for example, to care for contact lenses, which include one or more peptides and/or peptide derivatives as antimicrobial agents.

Various compositions, such as solutions, emulsions and suspensions are used in association with administering therapeutic components to the eyes. For example, an oil-in-water emulsion may be used as a carrier for a therapeutic component to be administered to the eyes.

At present, no safe effective preservative exists for an oil-in-water emulsion product. This is because the most acceptable preservative, benzalkonium chloride, loses its effectiveness due to partitioning into the oil phase. As a result only single dose containers of oil-in-water emulsion ophthalmic compositions can be marketed up to this time.

Use of single dose containers to store ophthalmic compositions prevents contamination and growth of microorganisms. However, single dose containers are inconvenient to use and are expensive for the consumer. Appropriate use of an effective preservative will allow for production of multidose containers of preserved ophthalmic compositions such as oil-in-water emulsions.

Various compositions are used in association with contact lenses to ensure that the lenses may be safely, comfortably and conveniently worn. Contact lens care compositions, for example, cleaning compositions, wetting compositions, conditioning compositions and the

like, often utilize at least one preservative, depending on the type of composition, for preserving the lens care composition itself.

A preserved contact lens care composition has sufficient antimicrobial activity so that when the composition is contacted with a contact lens substantially no increase in the microorganism population on the lens or in the composition is obtained. A preserved contact lens care composition may be termed a microbiostatic composition. Contact lens care compositions are often preserved to prevent any substantial increase in, or to gradually decrease, the population of contaminating microorganisms in the compositions and, thereby, to extend their shelf life.

Various compounds are known for use as preserving agents in preserved ophthalmic compositions. Examples include thimerosal, benzalkonium chloride and chlorhexidine. However, these preserving agents are known to exhibit ocular toxicity which may result in irritation or sensitivity to the eye. Further, a soft contact lens, a rigid gas permeable contact lens (RGP) or a hard contact lens can absorb or adsorb these compounds. This causes the contact lens to retain the irritating compound and contributes to the eye irritation and eye sensitivity which may result.

Thus, it is readily apparent that a continuing need exists for safe and efficacious compositions that can be used to preserve ophthalmic compositions.

Summary of the Invention

New preserved compositions and methods employing such compositions, particularly compositions and methods directed to eye care and contact lens care, have been discovered. The present compositions include effective preservatives to protect against growth of contaminating microorganisms. Importantly, such preserving activities are achieved using the present compositions with little or no risk of eye irritation or sensitivity.

In one embodiment of the invention, compositions useful for preserving ophthalmic compositions are provided. Such compositions include a magainin antimicrobial peptide, an analog of a magainin antimicrobial peptide or a mixture thereof present in an amount effective as a preservative. This effective amount may be less than about 10 milligrams per milliliter or less than about 1 milligram per milliliter or less than about 0.1 milligram per milliliter. Also included in the compositions is a therapeutic component. In a particularly useful embodiment of the invention, the compositions comprise magainin antimicrobial peptides. In another particularly useful embodiment of the invention, the compositions comprise an analog of a magainin antimicrobial peptide comprising the amino acid sequence GIGKFLKKAKKFGKAFVKILKK. The compositions may also include water and an effective amount of a buffer to provide the compositions with a desired pH. Also, the compositions may include an effective amount of a tonicity component to provide the compositions with a desired osmolality.

The compositions exist in various forms. For example, the compositions may be an oil-in-water emulsion, a solution or a suspension. Also, provided is for a sole preservative to be used in accordance with the invention.

The compositions may be applied onto or into the eyes. For example, the compositions may be used as a surgical irrigant.

In another embodiment of the invention, compositions useful for preserving ophthalmic compositions are provided. Such compositions include a magainin antimicrobial peptide, an analog of a magainin antimicrobial peptide or a mixture thereof present in an amount effective as a preservative. This effective amount may be less than about 10 milligrams per milliliter or less than about 1 milligram per milliliter or less than about 0.1 milligram per milliliter. In this embodiment, a sole preservative is used in the

compositions. In a particularly useful embodiment of the invention, the compositions comprise magainin antimicrobial peptides. In another particularly useful embodiment of the invention, the compositions comprise an analog of a magainin antimicrobial peptide comprising the amino acid sequence GIGKFLKKAKKFGKAFVKILKK. The compositions may also include water and an effective amount of a buffer to provide the compositions with a desired pH. Also, the compositions may include an effective amount of a tonicity component to provide the compositions with a desired osmolality.

The compositions exist in various forms. For example, the compositions may be an oil-in-water emulsion, a solution or a suspension.

The compositions may be applied onto or into the eyes. For example, the compositions may be used as a surgical irrigant.

In still another embodiment of the invention, compositions useful for preserving ophthalmic compositions are provided. Such compositions include a magainin antimicrobial peptide, an analog of a magainin antimicrobial peptide or a mixture thereof present in an amount effective as a preservative. This effective amount may be less than about 10 milligrams per milliliter or less than about 1 milligram per milliliter or less than about 0.1 milligram per milliliter. In this embodiment, the composition is an oil and water emulsion. In a particularly useful embodiment of the invention, the compositions comprise magainin antimicrobial peptides. In another particularly useful embodiment of the invention, the compositions comprise an analog of a magainin antimicrobial peptide comprising the amino acid sequence GIGKFLKKAKKFGKAFVKILKK. The compositions may also include water and an effective amount of a buffer to provide the compositions with a desired pH. Also, the compositions may include an effective amount of a tonicity component to provide the compositions with a desired osmolality.

The compositions may be applied onto or into the eyes. For example, the compositions may be used as a surgical irrigant.

In still another embodiment of the invention, compositions useful for preserving ophthalmic compositions are provided. Such compositions include an analog of a magainin antimicrobial peptide comprising the amino acid sequence GIGKFLKKAKKFGKAFVKILKK present in an amount effective as a preservative. This effective amount may be less than about 10 milligrams per milliliter or less than about 1 milligram per milliliter or less than about 0.1 milligram per milliliter. The compositions may also include water and an effective amount of a buffer to provide the compositions with a desired pH. Also, the compositions may include an effective amount of a tonicity component to provide the compositions with a desired osmolality.

The compositions may exist as a solution or a suspension.

The compositions may be applied onto or into the eyes.

In still another embodiment of the invention, compositions useful for preserving ophthalmic compositions are provided. Such compositions include a magainin antimicrobial peptide, an analog of a magainin antimicrobial peptide or a mixture thereof present in an amount effective as a preservative. This effective amount may be less than about 10 milligrams per milliliter or less than about 1 milligram per milliliter or less than about 0.1 milligram per milliliter. These compositions are applied onto or into the eyes. In a particularly useful embodiment of the invention, the compositions comprise magainin antimicrobial peptides. The compositions also may include water and an effective amount of a buffer to provide the compositions with a desired pH. Also, the compositions may include an effective amount of a tonicity component to provide the compositions with a desired osmolality.

Also provided for are methods of preserving ophthalmic compositions. One such method comprises contacting an ophthalmic composition with a magainin antimicrobial peptide, analogs of magainin antimicrobial peptides or mixtures thereof present in an amount effective as a preservative in the composition. In one embodiment, the composition is an oil and water emulsion.

Also provided for are methods for treating an eye. One such method comprises contacting an eye with a liquid medium which includes magainin antimicrobial peptides, analogs of magainin antimicrobial peptides or mixtures thereof in an amount effective as a preservative. In one embodiment, the composition is an oil and water emulsion.

The invention also provides for ophthalmic compositions which comprise magainin antimicrobial peptides, analogs of magainin antimicrobial peptides or mixtures thereof in an amount effective as a preservative. In a particularly useful embodiment of the invention, the compositions comprise an analog of a magainin antimicrobial peptide comprising the amino acid sequence GIGKFLKKAKKFGKAFVKILKK. Also in a preferred embodiment, the composition is an oil-in-water emulsion and the composition is provided in a multidose format.

Any and all features described herein and combinations of such features are included within the scope of the invention provided that such features of any such combination are not mutually exclusive.

These and other aspects and advantages of the present invention are apparent in the following detailed description and claims.

Detailed Description of the Invention

The present invention is applicable to preserving ophthalmic compositions, such as eye care compositions and contact lens care compositions which are benefited from being preserved.

One important feature of the compositions of the present invention is the inclusion of one or more antimicrobial peptides in the compositions.

In one embodiment, the present compositions include a sufficient amount of an antimicrobial peptide to effectively preserve the compositions. In a preferred embodiment, the antimicrobial peptide is a magainin antimicrobial peptide.

The antimicrobial peptides useful according to the present invention include naturally occurring antimicrobial peptides, preferably cytolytic peptides, synthetic antimicrobial peptides, antimicrobial peptide mimetics and nanotubes. Such peptides may be the L-form, the D-form or combinations or mixtures of both forms. At least some of these antimicrobial peptides may be membrane active. One or more of these antimicrobial peptides may act by disrupting a cell membrane.

Among the antimicrobial peptides preferably employed are those selected from defensins, peptides related to defensins, cecropins, peptides related to cecropins, and other amino acid polymers with antibacterial, antifungal and/or antiviral activities. Particularly preferred antimicrobial peptides employed in the present invention are magainin antimicrobial peptides and peptides related to magainin antimicrobial peptides and mixtures thereof.

Magainin antimicrobial peptides were first reported in the literature in 1987 (Zasloff (1987) Proc. Natl. Acad. Sci. USA 84, 5449-5453). Magainin antimicrobial peptides are a family of linear, amphipathic, cationic antimicrobial peptides, and are approximately 21 to 27 residues in length. It is believed that magainin antimicrobial peptides may exert their antimicrobial effect by disruption of cell membrane permeability.

Magainin antimicrobial peptides have numerous characteristics that make them a superior preservative for use in ophthalmic compositions. For example, magainin antimicrobial peptides are broad-spectrum

antimicrobial agents which exhibit cidal activity against Gram-negative and Gram-positive bacteria, fungi and protozoa. Also, magainin antimicrobial peptides display a reduced eye irritation compared to existing preservatives for ophthalmic compositions. For example, benzalkonium chloride is known to exhibit ocular toxicity which may result in irritation or sensitivity to the eye. In addition, magainin antimicrobial peptides are highly water-soluble allowing effective antimicrobial action in an oil-in-water emulsion. This high water solubility also minimizes loss of effectiveness due to adsorption to plastic containers. Further, numerous magainin antimicrobial peptides and magainin antimicrobial peptide derivatives are available which increases the opportunities for avoiding incompatibilities with specific drugs or excipients in a particular formulation of a composition of the invention. Still further, magainin antimicrobial peptides have a low degree of bacterial resistance, are effective at very low concentrations and are easily produced by chemical synthesis or heterologous gene expression. Because of these and other factors magainin antimicrobial peptides are very well suited for use in the present invention.

Exemplary magainin antimicrobial peptides include the peptides having the following amino acid sequences:

Magainin I
Gly Ile Gly Lys Phe Leu His Ser Ala Gly
Lys Phe Gly Lys Ala Phe Val Gly Glu Ile
Met Lys Ser (SEQ ID NO: 1)

Magainin II
Gly Ile Gly Lys Phe Leu His Ser Ala Lys
Lys Phe Gly Lys Ala Phe Val Gly Glu Ile
Met Asn Ser (SEQ ID NO: 2)

Exemplary magainin antimicrobial peptide analogs include the peptides having the following amino acid sequences:

MSI-78
Gly Ile Gly Lys Phe Leu Lys Lys Ala Lys
Lys Phe Gly Lys Ala Phe Val Lys Ile Leu
Lys Lys-NH_2 (SEQ ID NO: 3)

MSI-344
Gly Ile Gly Lys Phe Leu Lys Lys Ala Lys
Lys Phe Gly Lys Ala Phe Val Lys Ile Leu
Lys Lys (SEQ ID NO: 4)

Other useful magainin antimicrobial peptide analogs and derivatives include magainin antimicrobial peptides having N-terminal positively charged chain extensions (e.g., $(Lys)_{10}$-magainin which enhances the antimicrobial activity of the peptides).

Additional magainin antimicrobial peptides, magainin antimicrobial peptide analogs and derivatives which are contemplated for use according to the present invention are described in U.S. Patent Nos. 5,912,231, 5,847,047, 5,792,831, and 5,643,876 and in the publications Zasloff et al., Proc. Natl. Acad. Sci. USA 85, 910-913 (February 1988); Zasloff, Proc. Natl. Acad. Sci. USA 84, 5449-5453 (August 1987); and Bessale et al, Antimicrobial Agents, Chemotherapy 36 (No. 2), 313-317 (February 1992), and Maloy and Kari, Biopolymers 37, 105-122 (1995) each of which is incorporated in its entirety herein by reference.

Cecropins useful according to the invention include the peptides having the following amino acid sequences:

cecropin A:

Lys Trp Lys Leu Phe Lys Lys Ile Glu Lys
Val Gly Gln Asn Ile Arg Asp Gly Ile Ile
Lys Ala Gly Pro Ala Val Ala Val Val Gly
Gln Ala Thr Gln Ile Ala Lys (SEQ ID NO: 5);

and cecropin B:

Lys Trp Lys Val Phe Lys Lys Ile Glu Lys
Met Gly Arg Asn Ile Arg Asn Gly Ile Val
Lys Ala Gly Pro Ala Ile Ala Val Leu Gly
Glu Ala Lys Ala Leu Gly (SEQ ID NO: 6)

Cecropin D can also be employed.

Cecropin derivatives having C-terminus modifications, substitutions, and/or truncations which either enhance or do not inhibit antimicrobial activity are also contemplated for use according to the present invention. Useful derivatives include cecropin A amide (CA-NH_2), and cecropin A with a C-terminal ethylenediamine-modified homoserine (CA-Hse-NH-Et-NH_2). The general sequence homology of the N-terminus portion of the cecropins is necessary for activity and is therefore less suitable for truncation, modification, or substitution. However, analogs resulting from substitution of amino acids with similar chemical characteristics to the original can be designed. Maintaining an amphipathic helical structure similar to the original peptide will result in conservation of antimicrobial activity. An example of a substitution analog of cecropin B is Shiva-1:

Met Pro Arg Trp Arg Leu Phe Arg Arg Ile
Asp Arg Val Gly Lys Gln Ile Lys Gln Gly
Ile Leu Arg Ala Gly Pro Ala Ile Ala Leu
Val Gly Asp Ala Arg Ala Val Gly SEQ ID NO: 7).

Shiva-1 and other cecropin substitution analogs having antimicrobial activity are contemplated as being useful according to the invention.

Defensins useful according to the invention include: HNP-1 (human neutrophil peptide 1):

Ala Cys Tyr Cys Arg Ile Pro Ala Cys Ile
Ala Gly Glu Arg Arg Tyr Gly Thr Cys Ile
Tyr Gln Gly Arg Leu Trp Ala Phe Cys Cys
SEQ ID NO: 8);

HNP-2:

Cys Tyr Cys Arg Ile Pro Ala Cys Ile Ala
Gly Glu Arg Arg Tyr Gly Thr Cys Ile Tyr
Gln Gly Arg Leu Trp Ala Phe Cys Cys (SEQ ID NO: 9);

HNP-3:

Asp Cys Tyr Cys Arg Ile Pro Ala Cys Ile
Ala Gly Glu Arg Arg Tyr Gly Thr Cys Ile
Tyr Gln Gly Arg Leu Trp Ala Phe Cys Cys
(SEQ ID NO: 10);

NP-1 (rabbit neutrophil peptide 1):

Val Val Cys Ala Cys Arg Arg Ala Leu Cys
Leu Pro Arg Glu Arg Arg Ala Gly Phe Cys
Arg Ile Arg Gly Arg Ile His Pro Leu Cys
Cys Arg Arg (SEQ ID NO: 11);

and the BNP-1 (bovine neutrophil peptide) sequence:

Arg Leu Cys Arg Val Val Ile Arg Val Cys
Arg (SEQ ID NO: 12).

Other defensins and defensin analogs, such as those described in Selsted et al, J. Clin. Invest. 76, 1436-1439 (October 1985), and Kagan et al, Proc. Natl. Acad. Sci. USA 87, 210-214 (January 1990), each of which is incorporated in its entirety herein by reference, are also useful in the present invention.

Tachyplesins, such as tachyplesin I and II, and polyphemusins, such as polyphemusin I and II, are defensin-like peptides. See, e.g., Ohta et al,

Antimicrobial Agents and Chemotherapy 36 (No. 7), 1460-1465 (July 1992), which is incorporated in its entirety herein by reference. These peptides and antimicrobially active derivatives thereof are also contemplated as being useful in the present invention.

Other peptides, such as hybrids (peptides comprised of sequences from more than one antimicrobial class), e.g., cecropin-melittin hybrids, and peptide analogs in which one or more of the L-amino acids are replaced with other L-amino acids, can also be used with advantage provided that they retain sufficient antimicrobial activity.

Exemplary hybrid peptides include cecropin A-(1-8)-melittin-(1-18)-NH_2:

Lys Trp Lys Leu Phe Lys Lys Ile Gly Ile
Gly Ala Val Leu Lys Val Leu Thr Thr Gly
Leu Pro Ala Leu Ile Ser-NH_2 (SEQ ID NO: 13);

and cecropin A-(1-3)-melittin-(1-13)-NH_2:

Lys Trp Lys Gly Ile Gly Ala Val Leu Lys
Val Leu Thr Thr Gly Leu-NH_2 (SEQ ID NO: 14).

Melittin itself, however, is unsuitable for use due to its high toxicity.

Antimicrobial peptide mimetics are also contemplated for use with the present invention. Antimicrobial peptide mimetics may have a lower molecular weight than an average size antimicrobial peptide. These peptides may comprise components such as modified thiazole and/or oxazole moieties. Antimicrobial peptide mimetics may be membrane active molecules that function by disrupting cell membranes. At least one type of antimicrobial peptide mimetic can be obtained from Genaera Corp., Plymouth Meeting, PA.

The antimicrobial agents must be compatible with the composition being preserved. The antimicrobial peptides should also be non-toxic to humans.

Antimicrobial agents useful according to the present invention can be prepared using techniques well known to those skilled in the art. For example, antimicrobial peptides can be prepared by solid-phase synthesis or using heterologous gene expression. Exemplary processes for preparing antimicrobial peptides are given in Wade et al, Proc. Natl. Acad. Sci. USA 87, 4761-4765 (June 1990), Bessale et al, FEBS Letters 274, no. 1,2, 151-155 (November 1990), and Biochem. Biophys. Res. Commun. 277(3) 675-580 (November 2000) each of which is incorporated herein by reference in its entirety.

A second antimicrobial component can be employed in the present invention that is other than the first antimicrobial component. This second antimicrobial component can be selected from substantially non-oxidative antimicrobial components and mixtures thereof.

As used herein, substantially non-oxidative antimicrobial components include effectively non-oxidative organic chemicals, for example, synthetic polymers, which derive their antimicrobial activity through a chemical or physiochemical interaction with the microbes or microorganisms. Suitable non-oxidative antimicrobial components include, but are not limited to, quaternary ammonium salts used in ophthalmic applications such as poly[dimethylimino-2-butene-1,4-diyl] chloride, alpha- [4-tris(2-hydroxyethyl) ammonium]-dichloride (chemical registry number 75345-27-6, available under the trademark polyquarternium 1® from ONYX Corporation), benzalkonium halides, and biguanides such as salts of alexidine, alexidine-free base, salts of chlorhexidine, hexamethylene biguanides and their polymers, antimicrobial polypeptides, and the like and mixtures thereof. A particularly useful substantially non-oxidative antimicrobial component is selected from polyhexamethylene biguanide (PHMB), N-alkyl-2-pyrrolidone, chlorhexidine, polyquaternium-1, hexetidine, bronopol, alexidine, ophthalmically acceptable salts thereof and mixtures thereof.

The salts of alexidine and chlorhexidine can be either organic or inorganic and are typically gluconates, nitrates, acetates, phosphates, sulphates, halides and the like. Generally, the hexamethylene biguanide polymers, also referred to as polyaminopropyl biguanide (PAPB), have molecular weights of up to about 100,000. Such compounds are known and are disclosed in Ogunbiyi et al U.S. Patent No. 4,758,595, the disclosure of which is incorporated in its entirety herein by reference.

The substantially non-oxidative antimicrobial components useful in the present invention are preferably present in the liquid aqueous medium in concentrations in the range of about 0.000005% or about 0.00001% to about 2% (w/v).

More preferably the substantially non-oxidative antimicrobial component is present in the liquid aqueous medium at an ophthalmically acceptable or safe concentration.

The concentration of preservative selected depends, for example, on the effectiveness of the specific preservative in preventing growth, or the killing, of bacteria, fungi, and/or protozoa in a preserved composition. Concentration of preservative selected may also depend on the effectiveness of the specific preservative in reducing the microbial load on a contact lens.

The present compositions may conveniently be presented as solutions or suspensions in aqueous liquids or non-aqueous liquids, or as oil-in-water or water-in-oil liquid emulsions. The present compositions may include one or more additional ingredients which are conventionally employed in compositions of the same general type.

The present compositions in the form of aqueous suspensions may include excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropyl-

methylcellulose, sodium alginate, polyvinylpyrrolidone, gun tragacanth and gun acacia; dispersing or wetting agents may be a naturally occurring phosphatide, for example, lecithin, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadeca-ethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol mono-oleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example, polyoxyethylene sorbitan mono-oleate, and the like and mixtures thereof.

The present compositions in the form of oily suspensions may be formulated in a vegetable oil, for example, olive oil, castor oil, soy oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. Such suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol.

The present compositions may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example, castor oil, olive oil, soy oil, or arachis oil, or a mineral oil, for example, liquid paraffin, and the like and mixtures thereof. Suitable emulsifying agents may be naturally-occurring gums, for example, gum acacia or gum tragacanth, naturally-occurring phosphatides, for example, soya bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan mono-oleate, and condensation products of the said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan mono-oleate.

Also included within the scope of this invention are preserved compounds which increase in viscosity upon administration to the eye. For example, "gelling polysaccharides" which are disclosed in U.S. Patent No. 5,212,162 which is incorporated in its entirety herein by reference. Also disclosed in this patent are ophthalmic formulations containing carrageenans and

furcellarans which are administered as partially gelled liquids which gel upon instillation into the eye. Additionally, U.S. Patent Nos. 4,136,173, 4,136,177, and 4,136,178, disclose the use of therapeutic compositions containing xanthan gum and locust bean gum which are delivered in liquid form to the eye and which gel upon instillation. U.S. Patent No. 4,861,760 discloses ophthalmological compositions containing gellan gum which are administered to the eye as non-gelled liquids and which gel upon instillation. Each of these four patents is incorporated in its entirety herein by reference.

Also within the scope of this invention are preserved oils, ointments, gels and the like.

One or more additional components can be included in the present compositions based on the particular application for which the compositions are formulated. For example, the present compositions can be formulated to include a therapeutic component to be administered to the eyes. In one embodiment, the therapeutic component is an antibiotic. In a preferred embodiment, the antibiotic is cyclosporin A. In another embodiment, the therapeutic component is a steroid. In a preferred embodiment, the steroid is proednislone acetate. These are merely examples of therapeutic components that may be included in the compositions of the invention. Any therapeutic component that may advantageously be included in the present compositions is within the scope of this invention.

The present compositions may include components, such as cyclodextrins, to enhance the solubility of one or more other components included in the compositions. Cyclodextrins are widely known in the literature to increase the solubility of poorly water-soluble pharmaceuticals or drugs and/or enhance pharmaceutical/drug stability and/or reduce unwanted side effects of pharmaceuticals/drugs. For example, steroids, which are hydrophobic, often exhibit an increase in water solubility of one order of magnitude

or more in the presence of cyclodextrins. Any suitable cyclodextrin component may be employed in accordance with the present invention. The useful cyclodextrin components include, but are not limited to, those materials which are effective in increasing the apparent solubility, preferably water solubility, of poorly soluble active components and/or enhance the stability of the active components and/or reduce unwanted side effects of the active components. Examples of useful cyclodextrin components include, but are not limited to: β-cyclodextrin, derivatives of β-cyclodextrin, β-cyclodextrin, derivatives of β-cyclodextrin, β-cyclodextrin, derivatives of β-cyclodextrin, carboxymethyl- β-cyclodextrin, carboxymethyl-ethyl-β-cyclodextrin, diethyl-β-cyclodextrin, dimethyl-β-cyclodextrin, methyl-β-cyclodextrin, random methyl-β-cyclodextrin, glucosyl-β-cyclodextrin, maltosyl-β-cyclodextrin, hydroxyethyl-β-cyclodextrin, hydroxypropyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, and the like and mixtures thereof. As used herein, the term "derivatives" as it relates to a cyclodextrin means any substituted or otherwise modified compound which has the characteristic chemical structure of a cyclodextrin sufficiently to function as a cyclodextrin component, for example, to enhance the solubility and/or stability of active components and/or reduce unwanted side effects of the active components and/or to form inclusive complexes with active components, as described herein.

The specific cyclodextrin component selected should have properties acceptable for the desired application. The cyclodextrin component should have or exhibit reduced toxicity, particularly if the composition is to be exposed to sensitive body tissue, for example, eye tissue, etc. Very useful cyclodextrin components include beta-cyclodextrin, derivatives of β-cyclodextrin and mixtures thereof. Particularly useful cyclodextrin

components include sulfobutylether β-cyclodextrin, hydroxypropyl β-cyclodextrin and mixtures thereof. Sulfobutylether β-cyclodextrin is especially useful, for example, because of its substantially reduced toxicity.

The amount of cyclodextrin component in the present compositions should be effective to perform the desired function or functions in the present composition and/or perform the desired function or functions after administration to a human or animal. The amount of cyclodextrin component preferably is sufficient to complex at least in major amount, and more preferably substantially all, of the active component in the present composition. In one useful embodiment, the amount of cyclodextrin component in the present composition is in the range of about 0.1% to about 30% (w/v) or more of the composition.

An additional component or additional components included in the present compositions may be selected from components which are conventionally used in one or more contact lens care compositions. For example, the present compositions may be formulated as preserving compositions, disinfecting compositions, cleaning compositions, wetting compositions, conditioning compositions, soaking compositions and the like. Examples of such additional components include buffering agents, cleaning agents, wetting agents, sequestering agents, viscosity builders, tonicity agents, nutrient agents, contact lens conditioning agents, antioxidants, pH adjustors, and the like. These additional components are each included in the present compositions in an amount effective to impart or provide the beneficial or desired property to the compositions. For example, such additional components may be included in the present compositions in amounts similar to the amounts of such components used in other ophthalmic compositions.

Also, the present compositions may be formulated to be useful in performing two or more contact lens care operations. For example, for contact lens care, a

preserved disinfecting/cleaning composition, or a preserved cleaning/ conditioning composition or even an all-purpose lens care composition may be formulated and such multi-functional compositions are included within the scope of the present invention.

A surfactant component may be included in the present compositions. The surfactant component preferably is nonionic. Exemplary surfactant components include, but are not limited to, nonionic surfactants, for example, polysorbates (such as polysorbate 80-Trademark Tween 80), 4-(1, 1, 3, 3-tetramethylbutyl) phenol/poly(oxyethylene) polymers (such as the polymer sold under the trademark Tyloxapol), poly(oxyethylene)-poly(oxypropylene) block copolymers, glycolic esters of fatty acids and the like, and mixtures thereof. The surfactant may be selected from poly(oxyethylene)-poly(oxypropylene) block copolymers and mixtures thereof. Such surfactant components may be obtained commercially from the BASF Corporation under the trademark Pluronic®. Such block copolymers may be generally described as polyoxyethylene/polyoxypropylene condensation polymers terminated in primary hydroxyl groups.

The amount of surfactant component, if any, present varies over a wide range depending on a number of factors, for example, the specific surfactant or surfactants being used, the other components in the composition and the like. Often the amount of surfactant is in the range of about 0.005% or about 0.01% to about 0.1% or about 0.5% or about 1.0% or about 2.5% (w/v).

Useful buffering agents include, but not limited to, acetate buffers, citrate buffers, phosphate buffers and borate buffers. Acids and bases may be used to adjust the pH of the present compositions as needed.

Useful wetting agents include, but are not limited to, polyvinyl alcohol, polyoxamers, polyvinyl pyrrolidone, hydroxypropyl methyl cellulose and mixtures thereof.

Useful sequestering agents include, but are not limited to, disodium ethylene diamine tetraacetate, alkali metal hexametaphosphate, citric acid, sodium citrate and mixtures thereof.

Useful tonicity adjustors include, but are not limited to, sodium chloride, potassium chloride, mannitol, dextrose, glycerin, propylene glycol and mixtures thereof.

Useful viscosity builders include, but are not limited to, hydroxyethyl cellulose, hydroxypropyl methylcellulose, carboxymethyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol and mixtures thereof.

Useful antioxidants include, but are not limited to, sodium metabisulfite, sodium thiosulfate, N-acetylcysteine, butylated hydroxyanisole, butylated hydroxytoluene and mixtures thereof.

The present preserved compositions may be administered to the eyes. These compositions, formulated appropriately, may be used in place of prior conventional compositions. For example, the compositions may be use in administering a therapeutic component to the eyes. In one embodiment, an antibiotic is administered to the eyes in a composition of the invention. In another example, the compositions of the invention may be used as a surgical irrigant. These and other compositions of the present invention may be packaged in a multiple dose format container.

The present compositions may also be used in the care of a contact lens, for example, to make wearing the lens safe and comfortable. The present compositions, formulated appropriately, may be used in conventional contact lens care regimens by using the present compositions in place of prior conventional compositions. In many instances, these contact lens care regimens involve contacting the lens with the present composition in an amount, and at conditions, effective to obtain the beneficial or desired contact lens care result.

The following examples are set out to illustrate, but not limit, the scope of this invention.

EXAMPLE 1

The following composition is prepared by blending together the ingredients.

Ingredient	% w/v
Magainin	0.0001
Castor Oil	1.25
Glycerine	2.2
Polysorbate 80	1.0
Cyclosporin A	0.1
Carbomer (stabilizer)	0.05
Purified Water	Q.S. to 100%

This composition is formulated as and is effective as a compositon for the treatment of dry eye.

EXAMPLE 2

Thirty-four patients report symptoms of moderate to severe dry eye (grittiness, dryness, sensation that something is in the eye, tearing, burning). The patients are treated (eye drop) twice daily from a multidose container of the composition of Example 1. The treatment period is 12 weeks. After 8-12 weeks of treatment, improvements are seen in the dry eye symptoms of all the patients. All patients report improvements in the sandy, gritty feeling as well as improvements in dryness and itching. Improvements in the signs of dry eye are also noted when the patients are examined by an ophthalmologist (rose bengal staining of the cornea and superficial punctate keratitis).

There are no apparent adverse effects from the use of the magainin antimicrobial peptide containing composition of Example 1. For example, there is no bacterial overgrowth, and no increased risk of ocular infection demonstrated. The treatments are well

tolerated by the patients with no noted irritation or increased sensitivity.

EXAMPLE 3

The following composition is prepared by blending together the ingredients.

Ingredient	% w/v
Magainin	0.0001
Hydroxyethyl cellulose	0.65
Sodium chloride	0.67
Boric acid	0.39
Sodium borate decahydrate	0.20
Edetate disodium	0.127
Purified Water	Q.S. to 100%

This composition is formulated as and is effective as a preserved soft contact lens cleaning composition.

EXAMPLE 4

The following composition is prepared by blending together the ingredients.

Ingredient	% w/v
MSI-344	0.0001
Hydroxyethyl cellulose	0.65
Sodium chloride	0.67
Boric acid	0.39
Sodium borate decahydrate	0.20
Edetate disodium	0.127
Purified Water	Q.S. to 100%

This composition is formulated as and is effective as a preserved soft contact lens soaking/conditioning composition.

EXAMPLE 5

The following composition is prepared by blending together the ingredients.

<u>Ingredient</u>	<u>% w/v</u>
Hydroxypropyl beta-cyclodextrin	22.0
Prednisolone acetate	1.0
Hydroxypropylmethyl cellulose	0.25
Antimicrobial peptide mimetic	0.01
Sodium acetate	0.08
Hydrochloric acid	adjust to pH 4.5
Purified Water	Q.S. to 100%

This composition is formulated for and is effective for treatment of inflammatory disorders of the ocular tissue.